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(54) Title: STABILIZED EMULSION COMPOSITIONS

(57) Abstract: A water-in-oil emulsion for the topical delivery of a therapeutically effective active agent comprises a first emulsion agent selected from the group consisting of wax containing fatty acids, higher fatty acid, glycerol fatty acid ester, sorbitan fatty acid ester, oil, fat, and mixtures thereof; and a second emulsion agent selected from the group consisting of polyvalent metal ion compounds and mixtures thereof, and wherein the ratio of the first emulsion agent to the second emulsion agent is about 10:1 to 50:1.

STABILIZED EMULSION COMPOSITIONS

Field of the Invention

The present invention relates generally to external preparations for the skin, i.e., compositions for pharmaceutical and personal care applications such as skin care ointments and lotions, and in particular water-in-oil emulsion preparations for the skin.

Background of the Invention

In the cosmetic, pharmaceutical, or dermatological field, viscous compositions in the form of ointments, salves, creams and pastes having petroleum, lanolin, beeswax and the like as their base are well known. Difficulties have been exhibited with such compositions in that active ingredients or other ingredients thereof tend to separate and segregate with time. In addition, their viscosity tends to change with temperature and with time, and the contained ingredients are not always readily released for absorption by the skin or other surface upon which they are used.

Borax has been typically used in the prior art to neutralize the viscous oily materials for increased emulsion stability control in the water-in-oil emulsion system employing lanolin, beeswax and the like.

US Patent 4,190,568 discloses a mineral stabilized resin emulsion system such as asphalt emulsions, which can be utilized as a decorative and / or protective surface coating for roofing papers and the like. The emulsion system is a clay slurry emulsified by hydrocarbon resin, wax, or the like, and stabilized by a clay compound. Polyvalent metal ion compounds are added to the emulsion system to adjust the resin-material stabilizer slurry and react with any excess clay stabilizer, making the resultant dried emulsified films more water resistant.

Applicants have surprisingly found that polyvalent metal ion compounds, when added to external preparations for the skin having petroleum, lanolin, beeswax and the like as a base viscoelastic carrier, surprisingly provides a stable water-in-oil emulsion system that is comparable to the traditional borax water-in-oil emulsion systems of the prior art.

Summary of the Invention

This invention relates to a stabilized emulsion system formed as a water-in-oil emulsion for use in external preparations for the skin comprising: a) a first emulsion agent selected from the group consisting of wax containing a fatty acid, higher fatty acid, glycerol fatty acid ester, sorbitan fatty acid ester; oil, fat, and mixtures thereof, and b) a second emulsion agent selected from the group consisting of polyvalent metal ion compounds and mixtures thereof having a neutral or basic pH (of about 7 or above), and wherein the ratio of the first emulsion agent to the second emulsion agent is about 10:1 to 50:1. Preferably, the second emulsion agent is selected from the group consisting of hydroxides, sulfates and alkali metal salts containing an anion containing said polyvalent metal ion.

The invention also relates to a process for preparing a stable water-in-oil emulsion for use in external preparations for the skin comprising, comprising the steps of: a) combining an effective amount of: i) a first emulsion agent selected from the group consisting of consisting of wax, higher fatty acid, glycerol fatty acid ester, sorbitan fatty acid ester, oil, fat, and mixtures thereof; with ii) a second emulsion agent selected from the group consisting of polyvalent metal ion compounds and mixtures thereof having a neutral or basic pH (of about 7 or above); and b) emulsifying said combination; and wherein the ratio of the first emulsion agent to the second emulsion agent is about 10:1 to 50:1.

Detailed Description of the Invention

A water-in-oil emulsion generally comprises tiny colloid particles suspended in solution. The present invention provides a water-in-oil emulsion system which is reasonably stable, for use in preparations for the skin as viscoelastic vehicles for the delivery of the topically applied analgesics, skin moisteners, softeners and the like.

First Emulsion Agent: thickening ingredients. The first emulsion ingredient for use in the preparations of the present invention is in a liquid or solid form at ambient temperatures. It is viscous when it is in a liquid state, and has inflammability characteristics. Examples of oily ingredients include waxes containing fatty acids such as carnauba wax, spermacetti, beeswax and the like; higher fatty acids including lauric acid, myristic acid, palmitic acid, stearic acid, behenic acid, oleic acid, linolic acid, linolenic acid, lanolinic acid, isostearic acid and the like; glycerol fatty acid esters such as mono- and di-gylcerdies-stearates; sorbitan fatty acid esters such as sorbitan momolaurate and oleate; and oils and fats such as soy bean oil, rice barn oil, jojoba oil, avocado oil, almond oil, olive oil, cacao butter, sesame oil, parsic oil, castor oil, coconut oil, mink oil, and synthesized triglycerides such as glyceride myristate and 2-ethylhaxanoic glyceride.

A preferred thickening agent for us as the first emulsifying agent is beeswax. Beeswax, as its name implies, is typically obtained from bee honey combs and consists of esters of straight-chain monohydric alcohols with even numbered C_{12} - C_{26} carbon chains esterified with straight chain acids. Specific examples of the esters comprising beeswax are triacontanol hexadecanoate and hexacosonal hexacosanoate.

The first emulsion / thickening agent is employed in an amount from about 2 to 25% by weight of the finished preparation product of the present invention. A preferred range is about 5 to 15 wt. % of the finished preparation.

Second Emulsifying Agent: Polyvalent Metal Ion Compounds: It has been surprisingly and unexpectedly discovered that polyvalent metal ion compounds having a neutral or basic pH (of about 7 or above) can be combined or blended with the first emulsion agent, an oil or a wax, to provide a very stable emulsion system. Suitable polyvalent metal ion compounds for use as the second necessary emulsifying agent in the present invention include aluminum hydroxide, magnesium hydroxide, barium hydroxide, strontium hydroxide, calcium hydroxide, magnesium sulfate, sodium aluminate, sodium silicate, or mixtures thereof.

A preferred second emulsifying agent is sodium aluminate (aluminum sodium oxide: $AlNaO_2$), which is extremely soluble in water and produces a strongly alkaline aqueous solution.

The second emulsifying agent should be present in a sufficient amount to provide a stable water-in-oil emulsion system, i.e., a mixed film quality to the emulsion, for which ~~is~~ the theoretical amount is the quantity needed to neutralize the free acids in the first emulsifying agent. A preferred amount is about 2 to 10 wt. % of the first emulsifying agent, i.e., 0.04 to 2.5 wt. % of the finished preparation product of the present invention.

Oleaginous Base. The combined first and second emulsifying agents form a novel water-in-oil type emulsion useful as a delivery vehicle for pharmaceutically, cosmetically, or dermatologically active substances for various applications. The oily phase of the water-in-oil emulsion system of the present invention may further comprise one or more oily / oleaginous materials of wide ranging viscosities as a base to control the viscosity and hydrophobicity of the preparations of the present invention. Such base may include one or more members selected from the group consisting of mineral oils; vegetable oils; medium chain triglyceride (MCT) oil; various fatty acids; isopropyl

myristate; fatty alcohols; esters of sorbitol and fatty acids; oily sucrose esters; and in general any oily substance which is physiologically tolerated.

Mineral oils are generally preferred as the oleaginous base. The base is the major component of the finished preparation product and comprises from about 25.0 wt. % to 70 wt % of the total weight of the preparation.

The oleaginous base is typically supplemented with gel forming polymers, which are known per se, in order to increase the viscosity of the formulation.

Optional additives. In some applications, it is optional to further include a dispersant or emulsifier in addition to the above essential ingredients so that the oily ingredients forming the unmodified base can be dispersed or emulsified uniformly.

It is optional, but not necessary, to further add the traditional emulsifying agents in the prior art, e.g., borax, to neutralize the acids in the first emulsifying agent and further enhance the stability of the preparation of the present invention.

In addition to the optional emulsifying agents, humectants such as glycerin may also be added. Anti-foaming agents to minimize foaming of the preparations upon application to the skin such as high molecular weight silicones and other materials known in the art may also be added.

For pharmaceutical applications such as ointments, topical actives useful may include anti-inflammatories such as ibuprofen and piroxicam; antibiotics such as chloramphenicol; antifungal compounds such as nystatin and miconazole; anti-allergics such as pheniramide derivatives; antipuretics, topical analgesics, topical anesthetics; wound protectants, topical antiseptics and mixtures thereof. For the treatment of diaper rash and other skin irritations, zinc oxide is the preferred topical active.

For cosmetic applications, optional active ingredients may include anti-oxidants and free radical scavengers such as α-tocopherol; essential acids such as Complex Omega 6™ (manufactured by Seporga, Nice, France); sunscreen agents such as Parsol MCX™ or Parsol 1789™ (Givaudan, Switzerland).

To provide lubricity to a preparation without a greasy feel , additional emollients such as dimethicone may be incorporated in the ointment to further soften and moisturize the skin. The emollient may be incorporated in the preparations in an amount of from about 0.5 wt. % to 2.0 wt. % and preferably about 1.0 wt. %

Optionally, pigments may be present in the preparations in amounts of 0 to 20% by weight, with respect to the total weight of the emulsion, and preferably in amounts of 0.5 to 10%. They can be white or colored, inorganic and/or organic. Inorganic pigments and nanopigments include titanium, zirconium or cerium dioxides, as well as ~~of~~ zinc, iron or chromium oxides, nanometer-grade titanium oxides, ferric blue, pearlescent agents, such as mica covered with titanium oxide, with iron oxide, with natural pigment or with bismuth oxychloride, and colored titanium oxide-coated mica. Organic pigments include carbon black and barium, strontium, calcium and aluminum lakes.

Optional fillers may be present in the preparations in amounts of 0-20% by weight, and preferably 2-10% by weight. Fillers can be inorganic or synthetic, lamellar or non-lamellar such as talc, mica, silica, kaolin, nylon and polyethylene powders, teflon, starch, titanium oxide-coated mica, natural mother-of-pearl, boron nitride or microspheres, and silicone resin microbeads.

The emulsion may, depending on the applications, additionally comprise any additive commonly used such as dyes, fragrances, essential oils, preservatives, moisturizers, vitamins, essential fatty acids, sphingolipids, artificial tanning compounds

such as DHA, fat-soluble polymers, in particular hydrocarbons, such as polybutene or polyalkylenes, polyacrylates and silicone polymers which are compatible with fatty substances. The optional additives can be present in the preparations in the proportion of 0-10% by weight.

The emulsion systems according to the invention can constitute all or part of a preparation for the skin as a cosmetic, pharmaceutical, dermatological or hygienic composition. The preparations can be in the following forms: a care product for the body, face, scalp, and/or the hair, such as a cream, a paste, a lotion, or a gel; a cosmetic or dermatological product such as a sunscreen lotion.

The invention also relates to a process for the treatment of the skin, scalp and/or hair, characterized in that an emulsion or a composition as defined above is applied on the skin, scalp, and/or hair.

Preparation The components forming the preparations of the present invention are combined and dispersed by methods well known in the art, using any suitable means such as a motor-driven propeller or other suitable homogenizer-mixer. The dispersion is heated to a temperature above the melting point or pour point of the solid agents preferably while being agitated. It is preferred to heat the dispersion to a temperature of at least 10°C above the melting or pour point, and most preferably to about 15°C above the melting point or pour point of the solid agents. After the mixture of all components are thoroughly dispersed, the dispersion is removed from heat and cooled to a temperature at a rate effective to attain a desired vehicle viscosity for packaging in tubes, bottles or other forms known in the art.

The preparations employing the water-in-oil emulsion system of the present invention show surprising stability without showing any visible separation with long stable shelf life as commercial products, and are highly effective in topical applications.

Preparations employing the water-in-oil emulsion system of the present invention are comparable to the prior art water-in-oil emulsion system using borax as a stabilizing agent.

EXAMPLES Compositions employing the water-in-oil emulsion system of the present invention are characterized as being "cosmetically elegant" in panel tests, i.e., being uniformly smooth in feel, texture, and appearance. Embodiments of the compositions of the present invention are illustrated by the following representative examples.

Example 1. A cream skin care composition is prepared by adding into a suitable container 36.74 g. mineral oil, 5.5 g. anhydrous lanolin, 8.0 g. white wax, 4.57 g. paraffin hard wax, 7.0 g. synthetic beeswax, 1.0 g. glyceryl monostearate, 6.85 g. ceresine wax, and 15.0 zinc oxide. The mixture is heated to 70°C and stirred until uniform and then added with vigorous stirring to a mixture of 0.9 g sodium aluminate, 0.25 g. miconazole nitrate, 0.16 g. fragrance, 0.1 g. propylparaben and 13.93 g. deionized water at 70°C. The resulting emulsion is cooled to 50°C and 0.16 g. fragrance is added and the emulsion is cooled to 30°C. The resulting composition has the following formulation:

Ingredients	wt. %
mineral oil	36.74
Lanolin, anhydrous	5.5
White wax	8.0
Paraffin hard wax	4.57
Synthetic beeswax	7.0
Glyceryl monostearate	1.0
Ceresine wax	6.85
Zinc oxide	15.0
Sodium Aluminate	0.9
Miconazole nitrate	0.25
Fragrance	0.16
Propylparaben	0.10
water	qs to 100

Example 2 An exemplary lotion cream formulation with a chapped skin ameliorating effect is as follows:

Ingredients	wt. %
Solid paraffin	5.0
Beeswax	10.0
Vaseline	15.0
Liquid paraffin	41.0
Glycerin monostearate	2
Polyoxyethylene sorbitan monolaurate	2
Sodium aluminate	0.1
2-pentyl 5-β-D-glycopyranosyloxy-salicylate	0.05
3-methyl-1-butyl 4-β-D-glycopyranosyloxy-oxysalicylate	0.05
Perfume	q.s.
Sodium hydrogensulfite	0.03
Ethylparaben	0.3
water	balance

For the above formulation, the ingredients are mixed and held at 70°C so as to induce reaction of the oil phase and sodium aluminate. After the end of the reaction, the product was uniformly emulsified by a homomixer and thereafter the emulsion was cooled to 30°C under adequate stirring.

Example 3 A second exemplary lotion cream formulation with a chapped skin ameliorating effect prepared using the same method of Example 2 is as follows:

Ingredients	wt. %
Solid paraffin	5.0
Beeswax	10.0
Vaseline	15.0
Liquid paraffin	41.0
Glycerin monostearate	2
Sodium aluminate	0.1
Dodecyl 2-β-D-glucopyranosyloxy-5-hydroxybenzoate	0.05
Sodium hydrogensulfite	0.03
Ethylparaben	0.3
Perfume	q.s.
Water	Balance

Example 4 An exemplary make-up removal cleaning cream formulation follows:

Ingredients	wt. %
Beewax	14.0
Lanolin (cosmetic grade)	10.0
Mineral oil	40.0
Glyceryl Monostearate (self-emulsifying)	1.25
Polawax	0.5
water	Balance
Sodium Aluminate	1.3
Methylparaben	0.1
Perfume	qs
Color	qs
Oat flour	1.5

Beewax, lanolin, mineral oil, glyceryl monostearate, polawax and sodium aluminate are added into a container and heated while stirring to approximately 70°C. Deionized water, methylparaben and oat flour are then added to the oil phase mixture while stirring. The mixture is cooled to about 30°C, and then perfume and color are added.

Example 5 An exemplary liquid dandruff shampoo formulation is prepared from the following ingredients using conventional mixing techniques:

Ingredients	wt. %
Coconut oil	18
Castor oil	4
Potassium hydroxide	5.3
Glycerol	4
Perfume	0.2
Deionized water	qs 100
Sodium Aluminate	0.5
Niaciamide	4

Applicants intend to cover, in the appended claims, all modifications that are within the scope of the present invention.

CLAIMS

1. A stabilized emulsion system formed as a water-in-oil emulsion for use in external preparations for the skin comprising:

a) a first emulsion agent selected from the group consisting of wax containing fatty acids, higher fatty acid, glycerol fatty acid ester, sorbitan fatty acid ester, oil, fat, and mixtures thereof;

b) a second emulsion agent selected from the group consisting of polyvalent metal ion compounds and mixtures thereof, having a neutral or basic pH of about 7 or above; and

wherein the ratio of the first emulsion agent to the second emulsion agent is about 10:1 to 50:1.

2. An emulsion system according to claim 1, wherein the second emulsion agent is selected from the group consisting of hydroxides, sulfates and alkali metal salts containing an anion containing said polyvalent metal ion.

3. An emulsion system according to claim 2, wherein said second emulsion agent is selected from the group consisting of include aluminum hydroxide, magnesium hydroxide, barium hydroxide, strontium hydroxide, calcium hydroxide, magnesium sulfate, sodium aluminate, sodium silicate, or mixtures thereof.

4. A stabilized emulsion system according to any of claims 1 to 3, wherein said second emulsion agent is sodium aluminate.

5. A stabilized emulsion system according to any of claims 1 to 4, wherein the first emulsion agent is a wax containing fatty acids.

6. A stabilized emulsion system according to claim 5, wherein the first emulsion agent is beeswax.

7. A cosmetic, pharmaceutical, dermatological, or hygienic composition, comprising an effective amount of a water-in-oil emulsion system of any of claims 1 to 6.

8. A care product for the body, face, scalp, or hair, comprising an effective amount of a composition according to claim 7.

9. A cosmetic, pharmaceutical, dermatological, or hygienic composition of claim 7, further comprising an effective amount of an active compound delivered to the skin for the treatment thereof.

10. A cosmetic, pharmaceutical, dermatological, or hygienic composition of claim 9, wherein said active compound is selected from the group consisting of topically applied anesthetics, analgesics, antipuretics, astringents, anti-fungal compounds, antiseptics, skin wound protectants, sunscreening compounds, anti-inflammatories, antibiotics, anti-oxidants, anti-free radicals, skin protectants, and mixtures thereof.

11. A cosmetic, pharmaceutical, dermatological, or hygienic composition of claim 9 or claim 10, in the form of a cream, a gel, a shampoo, or a paste.

12. A process for preparing a stable water-in-oil emulsion for use in external preparations for the skin, said process comprising the steps of:

a) combining an effective amount of: i) a first emulsion agent selected from the group consisting of consisting of wax, higher fatty acid, glycerol fatty acid ester, sorbitan fatty acid ester, oil, fat, and mixtures thereof; with ii) a second emulsion

agent selected from the group consisting of polyvalent metal ion compounds and mixtures thereof having a neutral or basic pH of about 7 or above; and

b) emulsifying said combination; and

wherein the ratio of the first emulsion agent to the second emulsion agent is about 10:1 to 50:1.

13. The process of claim 12, wherein said second emulsion agent is selected from the group consisting of aluminum hydroxide, magnesium hydroxide, barium hydroxide, strontium hydroxide, calcium hydroxide, magnesium sulfate, sodium aluminate, sodium silicate, or mixtures thereof.

14. The process of claim 12, wherein said second emulsion agent is sodium aluminate.

15. The process of claim 12, wherein said first emulsion agent is beeswax.

16. Use of a stabilized emulsion system formed as a water-in-oil emulsion in the preparation of an external preparation for the skin, said emulsion system comprising:

a) a first emulsion agent selected from the group consisting of wax, higher fatty acid, glycerol fatty acid ester, sorbitan fatty acid ester, oil, fat, and mixtures thereof;

b) a second emulsion agent selected from the group consisting of polyvalent metal ion compounds and mixtures thereof having a neutral or basic pH of about 7 or above; and

wherein the ratio of the first emulsion agent to the second emulsion agent is about 10:1 to 50:1.

17. The use of claim 16, wherein said second emulsion agent is selected from the group consisting of include aluminum hydroxide, magnesium hydroxide, barium

hydroxide, strontium hydroxide, calcium hydroxide, magnesium sulfate, sodium aluminate, sodium silicate, or mixtures thereof.

18. The use of claim 16 or claim 17, wherein said first emulsion agent is beeswax.

19. The use of claim 15, wherein said second emulsion agent is sodium aluminate.

20. The use of any of claims 16 to 19, wherein said preparation for the skin further comprises an oily or oleaginous base selected from the group consisting of mineral oils; vegetable oils; medium chain triglyceride oil; various fatty acids; isopropyl myristate; fatty alcohols; esters of sorbitol and fatty acids; oily sucrose esters; and mixtures thereof.

21. The use of any of claims 16 to 20, wherein said oily or oleaginous base is present in an amount of about 25.0 wt. % to 70 wt % of the total weight of the preparation.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K7/48 A61K7/06 A61K7/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FR 2 575 385 A (SEDERMA SARL) 4 July 1986 (1986-07-04) page 3, line 1 - line 23; claims 1-4 ---	1-3, 5-13, 15-18,20
X	US 4 380 549 A (VAN SCOTT EUGENE J ET AL) 19 April 1983 (1983-04-19) claims 1-12; examples 15,16 ---	1-3, 5-13, 15-18, 20,21
X	US 4 284 630 A (YU RUEY J ET AL) 18 August 1981 (1981-08-18) claims 1-34; examples 8,9 --- -/--	1-3, 5-13, 15-18, 20,21

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"P" document published prior to the international filing date but later than the priority date claimed

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search	Date of mailing of the international search report
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 252 796 A (YU RUEY J ET AL) 24 February 1981 (1981-02-24) claims 1-34; examples 1,8,9,16,22,26,30-35,37,38,42,43,45,46,48	1-3, 5-13, 15-18, 20,21
X	GB 1 579 934 A (BEECHAM GROUP LTD) 26 November 1980 (1980-11-26) page 2, line 4-30; claims 1-5	1-3, 5-13, 15-18, 20,21
X	GB 1 489 133 A (BEECHAM GROUP LTD) 19 October 1977 (1977-10-19) page 1, line 50 - line 65; claims 1-5	1-3, 5-13, 15-18,20
X	GB 1 518 874 A (BEECHAM GROUP LTD) 26 July 1978 (1978-07-26) claims 1-3; example 2	1-3,5-8
X	GB 1 051 268 A (COLGATE-PALMOLIVE) claims 1-18; example 1	1-3,5-8
X	EP 0 077 630 A (BEECHAM GROUP PLC) 27 April 1983 (1983-04-27) claims 1-10; example 2	1-3, 5-13, 15-18,20
A	US 3 755 259 A (ANDERSON D) 28 August 1973 (1973-08-28)	

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 00/03941

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
FR 2575385 A	04-07-1986	NONE	
US 4380549 A	19-04-1983	US 4021572 A	03-05-1977
		US 4363815 A	14-12-1982
		US 4105783 A	08-08-1978
		US 4197316 A	08-04-1980
US 4284630 A	18-08-1981	NONE	
US 4252796 A	24-02-1981	NONE	
GB 1579934 A	26-11-1980	AU 514893 B	05-02-1981
		AU 2567677 A	07-12-1978
		CA 1099644 A	21-04-1981
		DE 2723682 A	20-04-1978
		ES 456212 A	01-05-1978
		FR 2367486 A	12-05-1978
		IT 1079696 B	13-05-1985
		ZA 7703115 A	26-04-1978
GB 1489133 A	19-10-1977	BE 867547 A	18-09-1978
		DE 2609575 A	30-09-1976
		FR 2303530 A	08-10-1976
		HK 11481 A	03-04-1981
		KE 3109 A	20-02-1981
		MY 24582 A	31-12-1982
GB 1518874 A	26-07-1978	AU 512597 B	16-10-1980
		AU 2399477 A	12-10-1978
		BE 853273 A	05-10-1977
		DE 2714753 A	27-10-1977
		DK 153477 A	07-10-1977
		FR 2347038 A	04-11-1977
		IE 44979 B	02-06-1982
		IT 1073240 B	13-04-1985
		JP 52125638 A	21-10-1977
		NL 7703638 A	10-10-1977
		SE 7703997 A	07-10-1977
		ZA 7701942 A	29-03-1978
GB 1051268 A		AU 4107164 A	19-08-1965
		BE 644855 A	07-09-1964
		CH 430058 A	15-02-1967
		DE 1301006 B	
		DK 113236 B	03-03-1969
		FR 1393607 A	07-07-1965
		NL 6402635 A	16-09-1964
		SE 302176 B	08-07-1968
EP 0077630 A	27-04-1983	AT 12730 T	15-05-1985
		DE 3263149 D	23-05-1985
US 3755259 A	28-08-1973	NONE	